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<p>(21) International Application Number: PCT/US98/04969 (22) International Filing Date: 13 March 1998 (13.03.98) (30) Priority Data: 08/818,766 14 March 1997 (14.03.97) US (71) Applicant: JAME FINE CHEMICALS, INC. [US/US]; 100 West Main Street, Bound Brook, NJ 08805 (US). (74) Agent: MATALON, Jack; 32 Shelley Road, Springfield, NJ 07081-2529 (US).</p>		<p>(81) Designated States: JP, KR, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: QUATERNARY SALTS OF 2-HYDROXY ACIDS (57) Abstract <p>Quaternary salts of 2-hydroxy acids with an alkanolamine such as monoethanolamine, diethanolamine or triethanolamine are useful for incorporation in skin and cosmetic formulations. The acid may contain 2 to 24 carbon atoms, preferably 2 to 17 carbon atoms. The monoethanolamine, diethanolamine and triethanolamine salts of 2-hydroxy acids such as glycolic, lactic, 2-hydroxydecanoic, 2-hydroxyoctanoic and 2-hydroxylauric acid are quite water-soluble and cosmetic formulations containing such salts are non-irritating to the skin.</p></p>		

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QUATERNARY SALTS OF 2-HYDROXY ACIDS

Background of the Invention

Alpha-hydroxy acids (i.e. 2-hydroxy acids) are known in the prior art. Such acids are used extensively in cosmetic formulations. However, there are a number of disadvantages associated with the use of such acids in cosmetic formulations. In particular, such acids are generally insoluble in water or other non-toxic solvents. Moreover, these acids can be highly corrosive effect to the skin.

10 Objects of the Invention

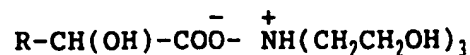
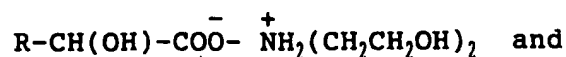
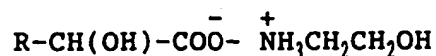
It is an object of the invention to provide 2-hydroxy acid compositions which will be highly soluble in water and other non-toxic solvents commonly used in cosmetic formulations (e.g. 1,3-butylene glycol).

15 It is a further object of the invention to provide 2-hydroxy acid compositions which will be less irritating to the skin than prior art 2-hydroxy acids when incorporated into cosmetic formulations.

Details of the Invention

20 The objects of the invention have been met by providing novel quaternary salts of 2-hydroxy acids. Such salts will be the quaternary salts of the 2-hydroxy acids with an alkanolamine which may be monoethanolamine, diethanolamine or triethanolamine.

25 The quaternary salts of the 2-hydroxy acids will have a formula selected from the group consisting of:



wherein R is hydrogen or a C₁-C₂₂, preferably C₃-C₁₅, alkyl group.

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The 2-hydroxy acid will generally be one which has 2 to about 24, preferably 2 to 17, carbon atoms. Preferable examples of such 2-hydroxy acids include glycolic acid, lactic acid, 2-hydroxydecanoic acid, 2-hydroxyoctanoic acid and
5 2-hydroxylauric acid.

The 2-hydroxy acid quaternary salts of the invention may be readily prepared as follows:

- (a) dissolve the selected 2-hydroxy acid in a non-reactive solvent;
- 10 (b) add an alkanolamine selected from the group consisting of monoethanolamine, diethanolamine and triethanolamine to the solution resulting from step (a); and
- (c) recover the quaternary salt from the reaction mixture resulting from step (b) or utilize the quaternary salt
15 in the form of a solution without recovery thereof.

In step (a), the choice of solvent is not critical so long as it is one which is non-reactive with the selected 2-hydroxy acid or the selected alkanolamine. Thus the solvent may be non-polar in nature such as methylene chloride, ethyl
20 acetate, n-hexane, n-heptane and the like; alternatively, the solvent may be polar in nature such as water or a non-toxic solvent such as isopropanol, 1,3-butylene glycol, isocetyl alcohol, etc. Preferably, the non-reactive solvent is non-polar in nature such as methylene chloride. Typically, 15 to
25 30 parts by weight of the selected 2-hydroxy acid will be utilized per 100 parts by weight of the selected non-polar solvent. Step (a) is conveniently carried out at temperatures of about 15 to 50°C.

In step (b), the selected alkanolamine is added, with
30 stirring, to the solution of the 2-hydroxy acid. Generally, the alkanolamine will be utilized in an amount corresponding to the stoichiometric amount required for the selected 2-hydroxy acid. Step (b) is also conveniently carried out at temperatures of about 15 to 50°C. The reaction between
35 the 2-hydroxy acid and the alkanolamine proceeds fairly

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quickly and is exothermic in nature. Therefore, cooling the reaction mixture to a temperature of about 25 to 35°C and adding the alkanolamine slowly, e.g. over a period of time of about 0.5 to 1 hour, is desirable.

- 5 In step (c), the quaternary salt will precipitate out if the selected solvent was non-polar in nature and is readily recovered by filtration. Typically, the salt will be washed with non-polar solvents such as methylene chloride and/or n-heptane to remove any unreacted components and thereafter
10 dried (in air and/or vacuum-dried at temperatures of about 40 to 70°C). Alternatively, if the selected solvent was a non-toxic polar solvent and it is desired to manufacture a solvent solution of the quaternary salt, the salt need not be recovered from the reaction mixture.
- 15 Typically, the yield of the quaternary salt will be nearly quantitative, e.g. 80-98% of theory. The quaternary salts of the 2-hydroxy acids of the invention will typically have a water solubility of about 15 to 30 wt.%.

The following examples shall serve to illustrate the invention. Unless otherwise indicated, all parts and percentages are on a weight basis.

Example 1

- A 3-liter, 3-neck flask was equipped with a stirrer, thermometer, condenser, addition funnel and a heating/cooling bath. 282 g (1.5 m) of 2-hydroxydecanoic acid were placed in the flask together with 1.5 kg of methylene chloride. Stirring was commenced and the temperature was adjusted to 30°C. 223.8 g (1.5 m) of triethanolamine was added, while stirring the reaction mixture, over a period of 1 hour, while
30 the temperature of the reaction mixture was maintained in the range of 27 to 33°C by external cooling.

The reaction mixture was stirred for an additional two hours, while maintaining the temperature at 35°C. The reaction

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mixture was then cooled to 20°C and the precipitate was collected by filtration. The product (i.e. the precipitate) was washed with 500 g methylene chloride and thereafter washed with 300 g of n-heptane. The product was air-dried
5 for several hours and thereafter dried under vacuum at 50-60°C for 4 hours. The product yield was 481 g (95% of theory). The product was soluble in water in excess of 20 wt.%.

Example 2

10 Example 1 was repeated using 188 g (1.0 m) of 2-hydroxy-decanoic acid, 940 g methylene chloride and 105 g (1.0 m) of diethanolamine. After working up the product in the same manner, 273 g of product (93.2% of theory) was obtained. The product was soluble in water in excess of 20 wt.%.

Example 3

15 Example 1 was repeated using 160 g (1.0 m) 2-hydroxyoctanoic acid, 1.0 kg methylene chloride and 149.2 g (1.0 m) of triethanolamine. After working up the product in the same manner, 290 g of product (94% of theory) was obtained. The
20 product was soluble in water in excess of 20 wt.%.

Example 4

Example 3 was repeated using 105 g (1.0 m) of diethanolamine instead of the triethanolamine. 236 g (89% of theory) of product was obtained. The product was soluble in water in
25 excess of 20 wt.%.

Example 5

Example 1 was repeated using a 1-liter, 3-neck flask. 25.33 g (0.33 m) of glycolic acid was dissolved in 200 ml ethyl acetate at a temperature of 35-45°C. Thereafter,
30 49.7 g (0.33 m) of triethanolamine was added over a period of one hour and stirring was continued for 2 hours at 40°C. 69 g (92% of theory) of product having a solubility in water in excess of 20 wt.% were obtained.

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Example 6

Example 1 was repeated using 212 g (1.0 m) of 2-hydroxylauric acid, 1.5 kg methylene chloride and 149.2 g (1.0 m) triethanolamine). 346 g (95.8% of theory) of product having a solubility in water in excess of 20 wt.% were obtained.

Example 7

Example 6 was repeated using 105 g (1.0 m) of diethanolamine instead of the triethanolamine. 346 g (95.8% of theory) of product having a solubility in water in excess of 20 wt.% were obtained.

Example 8

Example 1 was repeated using a 1-liter, 3-neck flask. 29.5 g of 85% d-l lactic acid (0.28 m) was dissolved in 150 g of isopropanol at a temperature of 35-45°C. Thereafter, 41.7 g (0.28 m) of triethanolamine was added over a period of one hour and stirring was continued for 2 hours at 35°C. The reaction mixture was cooled to 5°C and the product was filtered and washed with isopropanol and thereafter vacuum-dried. 56 g (84% of theory) of product having a solubility in water in excess of 20 wt.% were obtained.

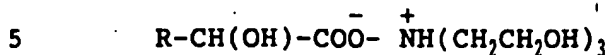
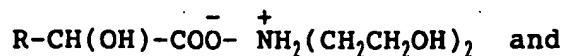
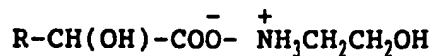
Example 9

Example 3 was repeated using 100 g (0.625 m) 2-hydroxy-octanoic acid, 550 g methylene chloride and 38.2 g (0.625 m) of monoethanolamine. After working up the product in the same manner, 121 g of product (87.6% of theory) was obtained. The product was soluble in water in excess of 20 wt.%.

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WHAT IS CLAIMED IS:

1. A quaternary salt of a 2-hydroxy acid having the formula selected from the group consisting of:



wherein R is hydrogen or a C₁-C₂₂ alkyl group.

2. The salt of claim 1 wherein R is hydrogen.

3. The salt of claim 1 wherein R is a C₃-C₁₅ alkyl group.

4. The salt of claim 1 wherein the 2-hydroxy acid is selected from the group consisting of glycolic acid, lactic acid, 2-hydroxydecanoic acid, 2-hydroxyoctanoic acid and 2-hydroxylauric acid, and the alkanolamine is selected from
5 the group consisting of monoethanolamine, diethanolamine and triethanolamine.

5. The salt of claim 1 comprising the quaternary salt of glycolic acid with monoethanolamine.

6. The salt of claim 1 comprising the quaternary salt of glycolic acid with diethanolamine.

7. The salt of claim 1 comprising the quaternary salt of glycolic acid with triethanolamine.

8. The salt of claim 1 comprising the quaternary salt of lactic acid with monoethanolamine.

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9. The salt of claim 1 comprising the quaternary salt of lactic acid with diethanolamine.

10. The salt of claim 1 comprising the quaternary salt of lactic acid with triethanolamine.

11. The salt of claim 1 comprising the quaternary salt of 2-hydroxydecanoic acid with monoethanolamine.

12. The salt of claim 1 comprising the quaternary salt of 2-hydroxydecanoic acid with diethanolamine.

13. The salt of claim 1 comprising the quaternary salt of 2-hydroxydecanoic acid with triethanolamine.

14. The salt of claim 1 comprising the quaternary salt of 2-hydroxyoctanoic acid with monoethanolamine.

15. The salt of claim 1 comprising the quaternary salt of 2-hydroxyoctanoic acid with diethanolamine.

16. The salt of claim 1 comprising the quaternary salt of 2-hydroxyoctanoic acid with triethanolamine.

17. The salt of claim 1 comprising the quaternary salt of 2-hydroxylauric acid with monoethanolamine.

18. The salt of claim 1 comprising the quaternary salt of 2-hydroxylauric acid with diethanolamine.

19. The salt of claim 1 comprising the quaternary salt of 2-hydroxylauric acid with triethanolamine.

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US98/04969
A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/205, 31/19, 31/20

US CL : 514/554, 557, 558; 554/103, 108, 109, 110; 564/281, 291, 292

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,105,782 A (YU et al.) 08 August 1978, entire document especially column 1, lines 36-44, column 4 and examples 1-5.	1-10
X	US 4,363,815 A (YU et al.) 14 December 1982, entire document, especially column 4, lines 1-10	1-19

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 ☐ See patent family annex.

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